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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

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Manufacture of trimethylhydroquinone diacylates

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Manufacture of Trimethylhydroquinone Diacylates

The present invention is concerned with a process for the manufacture of 2,3,5-trimethylhydroquinone diacylates.

The products of the process are useful as reactants for the manufacture of 2,3,5-trimethylhydroquinone, itself a known valuable reactant for the manufacture of (all-rac)-α-tocopherol, the most active member of the vitamin E group.

2,3,5-Trimethylhydroquinone diacylates are known to be producible by reacting ketoisophorone with an acylating agent in the presence of a catalyst. Many such catalysts have been proposed in the past for this purpose, in particular protonic acids, e.g. such inorganic acids as sulphuric acid; such organic acids as p-toluenesulphonic acid; strongly acidic ion exchange resins; and such Lewis acids as zinc chloride, boron trifluoride, antimony pentafluoride and titanium tetrachloride: see inter alia German Offenlegungsschrift 2149159 and European Patent Publications EP 0916642 A1 and EP 1028103 A1. The known procedures, depending on the particular catalyst used, entail certain disadvantages such as cost and lack of stability of the catalyst, use of chlorinated compounds, unsatisfying yield and formation of by-products, e.g., catechol diacetate.

In accordance with the present invention it has been found that the conversion of ketoisophorone to 2,3,5-trimethylhydroquinone diacylates can be advantageously accomplished by the use of an indium salt as a catalyst.

Accordingly, the present invention provides a process for the manufacture of a 2,3,5-trimethylhydroquinone diacylates, which process comprises reacting ketoisophorone with an acylating agent in the presence of an indium salt as a catalyst.

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The indium salt used as the catalyst in the process of the present invention is suitably an indium(III) halide (e.g. indium trichloride, tribromide or triiodide) or indium(III) triflate [$In(SO_3CF_3)_3$] and may be present in an amount of from about 0.1 mol-% to about 2 mol-%, preferably in an amount of about 0.1 to about 1 mol-%, based ketoisophorone. The catalyst may be added to the reaction mixture in solid form, anhydrous or hydrated (of which $InCl_3 \cdot 4\ H_2O$ is an example).

The acylating agent used in the process of the present invention may be any acylating agent that is conventionally used in the conversion of ketoisophorone to 2,3,5-trimethylhydroquinone acylates, particularly acid anhydrides, acyl halides, and enol esters. Examples of acid anhydrides are straight or branched chain alkanoic acid anhydrides such as acetic, propionic and butyric anhydride. Examples of acyl halides are straight or branched chain alkanoyl chlorides such as acetyl, propionyl and butyryl chloride. Finally, examples of enol esters are isopropenyl acetate and butyrate. The preferred acylating agent is acetic anhydride or acetyl chloride, especially acetic anhydride.

The process of the present invention can be carried out in the presence or in the absence of a solvent. As a solvent, any inert polar or non-polar organic solvent or any mixture of two or more of such solvents can be used. Suitable classes of polar organic solvents include aliphatic and cyclic ketones, e.g. diethyl ketone and isobutyl methyl ketone and, respectively, cyclopentanone and isophorone; and aliphatic and cyclic esters, e.g. ethyl acetate and isopropyl acetate, and, respectively, γ-butyrolactone, ethylene carbonate and propylene carbonate. As suitable classes of non-polar organic solvents there may be mentioned aliphatic hydrocarbons, e.g. hexane, heptane and octane, and aromatic hydrocarbons, e.g. benzene, toluene and the xylenes. The reaction can be effected in a single solvent phase, e.g. in toluene alone as the solvent, or in a biphasic solvent system, e.g. in ethylene or propylene carbonate and heptane. In a preferred aspect of the invention, the reaction is carried out in the absence of a solvent.

While the ratio of acylating agent to ketoisophorone is not narrowly critical the ratio of acylating agent (equivalents) to ketoisophorone (moles) is suitably from about 1 : 1 to about 5 : 1, preferably from about 2 : 1 to about 3 : 1, and is most preferably about 3 : 1.

The process of the invention is conveniently carried out at temperatures from about 0°C to about 140°C, preferably from about 25°C to about 90°C, especially from about 25°C to about 70°C.

Moreover, the process is conveniently carried out under an inert gas atmosphere, preferably under gaseous nitrogen or argon.

The progress of the reaction is suitably monitored by gas chromatography and mass spectrometry of samples taken from the reaction mixture at various time intervals during the reaction.

The produced 2,3,5-trimethylhydroquinone diacylate can be isolated after distilling off the remaining acylating agent and the secondary product formed in the acylation, e.g. acetic acid when acetic anhydride is used as the acylating agent, by extraction of the crude product mixture with a suitable organic solvent, e.g. toluene. Another isolation procedure is the crystallization of the 2,3,5-trimethylhydroquinone diacylate from the mixture at the termination of the reaction by cooling, and, optionally, adding water, to the mixture to promote the crystallization.

The catalyst can be recovered by extraction with water or acid-water and concentration of the extract. Alternatively, the catalyst can be recovered by adding a biphasic solvent system, e. g. a carbonate (particularly ethylene carbonate or propylene carbonate) and an aliphatic hydrocarbon (particularly heptane or octane), and isolating it from the polar (carbonate) phase.

The 2,3,5-trimethylhydroquinone diacylate obtained by the process of the present invention can be converted into 2,3,5-trimethylhydroquinone by transesterification, i.e. by treatment with an alcohol, e.g. an aliphatic alcohol such as isopropanol or n-butanol. Depending on the amounts of alcohol and catalyst and on the temperature in the reaction mixture, the transesterification yields the unesterified 2,3,5-trimethylhydroquinone and the ester formed as the further product. The former product can be converted into (all-rac)-α-tocopherol by reaction with isophytol, preferably in a biphasic solvent system, e.g. in a solvent system comprising a polar solvent such as ethylene or propylene carbonate, and an non-polar solvent, particularly an aliphatic hydrocarbon such as heptane.

The invention is illustrated by the following Example.

Example

A 230-ml four-necked flat-bottomed flask with heating/cooling jacket equipped with a thermometer, a glass-tube for Ar-purge, a reflux condenser and a mechanical stirrer was filled with the catalyst (see table below) and 20.65 g (133 mmol) of ketoisophorone and a yellow solution was obtained. Within 10 min 40.64 g (400 mmol, 37.60 ml) of acetic anhydride were added with stirring. During addition, the mixture turned dark yellow to finally dark brown. The internal temperature was regulated by a thermostat. Samples were withdrawn and submitted to qualitative GC-analysis. The results are tabulated below :

Catalyst (mol%)	Temperature (°C)	Reaction time (hr)	Conversion (%)	Purity (%)		
				KIP	TMHQ -DA	TMC -DA
$InCl_3$ (1)	25	18	23.9	76.1	7.2	1.6
$InCl_3$ (1)	50	21	45.5	54.6	37.2	5.8
$InCl_3$ (1)	50	37[a]	50.0	50.0	42.3	6.6
$InCl_3$ (2+1)[b]	50	76[b]	78.9	21.1	68.3	10.0
$In(SO_3CF_3)_3$ (1)	50	5	100.0	0.0	93.5	6.8
$In(SO_3CF_3)_3$[a] (0.1)	50	10[a]	65.3	34.7	58.5	4.1

KIP = ketoisophorone; TMHQ-DA = 2,3,6-trimethylhydroquinone diacetate; TMC-DA = 2,3,6-trimethyl catechol diacetate. The molar ratio of Ac_2O/KIP was 3/1. The amount of catalyst is based on KIP. [a] Inhibition of the reaction after the indicated time. [b] 1 mol% of catalyst was added after 76 hrs as inhibition of the reaction occurred but no progress was observed after this addition.

Claims

1. A process for the manufacture of a 2,3,5-trimethylhydroquinone diacylate comprising reacting ketoisophorone with an acylating agent in the presence of an indium salt as a catalyst.

2. A process according to claim 1, wherein the indium salt is indium trichloride or indium tris (trifluoromethanesulfonate).

3. A process according to any one of claims 1 to 3, wherein the acylating agent is an acid anhydride, an acyl halide or an enol ester.

4. A process according to claim 3, wherein the acylating agent is a straight or branched chain alkanoic acid anhydride, preferably acetic, propionic or butyric anhydride; a straight or branched chain alkanoyl chloride, preferably acetyl, propionyl or butyryl chloride; or, as an enol ester, isopropenyl acetate or butyrate.

5. A process according to any one of claims 1 to 8, wherein the ratio of acylating agent (equivalents) to ketoisophorone (moles) is from about 1 : 1 to about 5 : 1, preferably about 2 : 1 to about 3 : 1, most preferably about 3 : 1.

6. A process according to any one of claims 2 to 9, wherein the amount of catalyst used is from about 0.1 mol-% to about 2 mol-%, preferably in an amount from about 0.1 to about 1 mol-%, based ketoisophorone.

7. A process according to any one of claims 1 to 12, wherein the acylating reaction is carried out at from about 0°C to about 140°C, preferably from about 25°C to about 90°C, especially from about 25°C to about 70°C.

8. A process according to any one of claims 1 to 13, wherein the 2,3,5-trimethylhydroquinone diacylate obtained is converted into (all-rac)-α-tocopherol by transesterification to yield 2,3,5-trimethylhydroquinone and reaction of the latter with isophytol.